# GLEEVEC™ (imatinib mesylate) Capsules

NDA 21-335

# DRAFT Package Insert

GLEEVEC™ Capsules

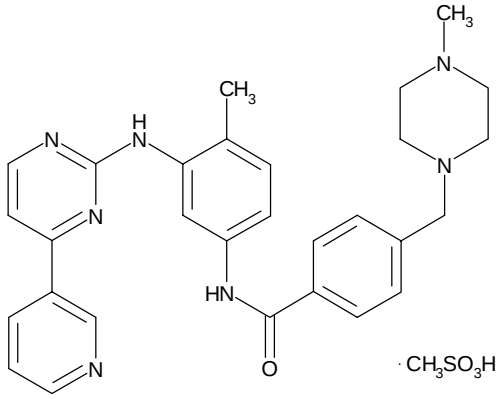
(imatinib mesylate)

Rx only

**Prescribing Information**

# DESCRIPTION

GLEEVEC™ capsules contain imatinib mesylate equivalent to 100 mg of imatinib free base. Imatinib mesylate is designated chemically as 4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-phenyl]benzamide methanesulfonate and its structural formula is:




Imatinib mesylate is a white to off-white to brownish or yellowish tinged crystalline powder. Its molecular formula is $C_{29}H_{31}N_7O \cdot CH_4SO_3$ and its relative molecular mass is 589.7. Imatinib mesylate is very soluble in water and soluble in aqueous buffers ≤ pH 5.5 but is very slightly soluble to insoluble in neutral/alkaline aqueous buffers. In non-aqueous solvents, the drug substance is freely soluble to very slightly soluble in dimethyl sulfoxide, methanol and ethanol, but is insoluble in n-octanol, acetone and acetonitrile.

Inactive ingredients: colloidal silicon dioxide (NF), crospovidone (NF), magnesium stearate (NF) and microcrystalline cellulose (NF). Capsule shell: gelatin, iron oxide, red (E172); iron oxide, yellow (E172); titanium dioxide (E171).

# CLINICAL PHARMACOLOGY

## Mechanism of Action

Imatinib mesylate is a protein-tyrosine kinase inhibitor that inhibits the Bcr-Abl tyrosine kinase, the constitutive abnormal tyrosine kinase created by the Philadelphia chromosome abnormality in chronic myeloid leukemia (CML). It inhibits proliferation and induces apoptosis in Bcr-Abl positive cell lines as well as fresh leukemic cells from Philadelphia chromosome positive chronic myeloid leukemia. In colony formation assays using *ex vivo* peripheral blood and bone marrow samples, imatinib shows inhibition of Bcr-Abl positive colonies from CML patients.

*In vivo*, it inhibits tumor growth of Bcr-Abl transfected murine myeloid cells as well as Bcr-Abl positive leukemia lines derived from CML patients in blast crisis.

I*n vitro* studies demonstrate imatinib is not entirely selective; it also inhibits the receptor tyrosine kinases for platelet-derived growth factor (PDGF) and stem cell factor (SCF), c-Kit, and inhibits PDGF- and SCF-mediated cellular events

## Pharmacokinetics

The pharmacokinetics of GLEEVEC have been evaluated in studies in healthy subjects and in population pharmacokinetic studies in over 500 patients. Imatinib is well absorbed after oral administration with $C_{max}$ achieved within 2-4 hours post-dose. Mean absolute bioavailability for the capsule formulation is 98%. Following oral administration in healthy volunteers, the elimination half-lives of imatinib and its major active metabolite, the N-desmethyl derivative, were approximately 18 and 40 hours, respectively. Mean imatinib AUC increased proportionally with increasing dose in the range 25-1000 mg. There was no significant change in the pharmacokinetics of imatinib on repeated dosing, and accumulation is 1.5-2.5 fold at steady state when GLEEVEC is dosed once daily. At clinically relevant concentrations of imatinib, binding to plasma proteins in *in vitro* experiments is approximately 95%, mostly to albumin and $\alpha_1$-acid glycoprotein.

Metabolism and elimination

CYP3A4 is the major enzyme responsible for metabolism of imatinib. Other cytochrome P450 enzymes, such as CYP1A2, CYP2D6, CYP2C9, and CYP2C19, play a minor role in its metabolism. The main circulating active metabolite in humans is the N-demethylated piperazine derivative, formed predominantly by CYP3A4. It shows *in vitro* potency similar to the parent imatinib. The plasma AUC for this metabolite is about 15% of the AUC for imatinib.

Elimination is predominately in the feces, mostly as metabolites. Based on the recovery of compound(s) after an oral $^{14}$C-labelled dose of imatinib, approximately 81% of the dose was eliminated within 7 days, in feces (68% of dose) and urine (13% of dose). Unchanged imatinib accounted for 25% of the dose (5% urine, 20% feces), the remainder being metabolites.

Typically, clearance of imatinab in a 50 year old patient weighing 50 kg is expected to be 8 L/h, while for a 50 year old patient weighing 100 kg the clearance will increase to 14 L/h. However, the inter-patient variability of 40% in clearance does not warrant initial dose adjustment based on body weight and/or age but indicates the need for close monitoring for treatment related toxicity.

### Special Populations

Pediatric: There are no pharmacokinetic data in pediatric patients.

Hepatic Insufficiency: No clinical studies were conducted with GLEEVEC in patients with impaired hepatic function.

Renal Insufficiency: No clinical studies were conducted with GLEEVEC in patients with decreased renal function (studies excluded patients with serum creatinine concentration more than 2 times the upper limit of the normal range). Imatinib and its metabolites are not significantly excreted via the kidney.

### Drug-Drug Interactions

CYP3A4 inhibitors: There was a significant increase in exposure to imatinib (mean $C_{max}$ and AUC increased by 26% and 40%, respectively) in healthy subjects when GLEEVEC was co-administered with a single dose of ketoconazole (a CYP3A4 inhibitor). (see PRECAUTIONS)

CYP3A4 substrates: Imatinib increased the mean Cmax and AUC of simvastatin (CYP3A4 substrate) by 2- and 3.5- fold, respectively, indicating an inhibition of CYP3A4 by imatinib. (See PRECAUTIONS)

CYP3A4 inducers: No formal study of CYP3A4 inducers has been conducted, but a patient on chronic therapy with phenytoin (a CYP3A4 inducer) given 350 mg daily dose of Gleevec had an $AUC_{0-24}$ about one fifth of the typical $AUC_{0-24}$ of 20 μg•h/mL. This probably reflects the induction of CYP3A4 by phenytoin. (see PRECAUTIONS)

In vitro studies of CYP enzyme inhibition: Human liver microsome studies demonstrated that imatinib is a potent competitive inhibitor of CYP2C9, CYP2D6, and CYP3A4/5 with $K_i$ values of 27, 7.5, and 8 μM, respectively. Imatinib is likely to increase the blood level of drugs that are substrates of CYP2C9, CYP2D6 and CYP3A4/5. (see PRECAUTIONS)

## CLINICAL STUDIES

Three international, open-label, single-arm studies were conducted in patients with Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML): 1) in the chronic phase after failure of interferon-alfa (IFN) therapy, 2) in accelerated phase disease, or 3) in myeloid blast crisis. About 45% of patients were women and 6% were black. In clinical studies 38-40% of patients were ≥ 60 years of age and 10-12% of patients were ≥ 70 years of age.

*Chronic phase, prior Interferon-treatment:* 532 patients were treated at a starting dose of 400 mg; dose escalation to 600 mg was allowed. The patients were distributed in three main categories according to their response to prior interferon: failure to achieve (within 6 months) or loss of a complete hematologic response (29%), failure to achieve (within 1 year) or loss of a major cytogenetic response (35%), or intolerance to interferon (36%). Patients had received a median of 14 months of prior IFN therapy at doses ≥ 25 $x10^6$ IU/week and were all in late chronic phase, with a median time from diagnosis of 32 months. Effectiveness was evaluated on the basis of the rate of hematologic response and by bone marrow exams to assess the rate of major cytogenetic response (up to 35% Ph+ metaphases) or complete cytogenetic response (0% Ph+ metaphases). Efficacy results are reported in Table 1. Results were similar in the three subgroups described above.

*Accelerated phase*: 235 patients with accelerated phase disease were enrolled. These patients met one or more of the following criteria ≥15% - <30% blasts in PB or BM; ≥30% blasts + promyelocytes in PB or BM; ≥20% basophils in PB; <100 x $10^9$ /L platelets. The first 77 patients were started at 400 mg, with the remaining 158 patients starting at 600 mg.

Effectiveness was evaluated primarily on the basis of the rate of hematologic response, reported as either complete hematologic response, no evidence of leukemia (i.e., clearance of blasts from the marrow and the blood, but without a full peripheral blood recovery as for complete responses), or return to chronic phase CML. Cytogenetic responses were also evaluated. Efficacy results are reported in Table 1. Although hematologic response rates were similar for patients receiving 600 mg and 400 mg, major cytogenetic responses were more frequent for the former (24% and 16% respectively).

*Myeloid blast crisis:* 260 patients with myeloid blast crisis were enrolled. These patients had ≥30% blasts in PB or BM and/or extramedullary involvement other than spleen or liver; 165 (63%) had received prior chemotherapy for treatment of either accelerated phase or blast crisis ("pretreated patients") whereas 95 (37%) had not ("untreated patients"). The first 37 patients were started at 400 mg; the remaining 223 patients were started at 600 mg.

Effectiveness was evaluated primarily on the basis of rate of hematologic response, reported as either complete hematologic response, no evidence of leukemia, or return to chronic phase CML using the

same criteria as for the study in accelerated phase. Cytogenetic responses were also assessed. Efficacy results are reported in Table 1. The hematologic response rate was higher in untreated patients than in treated patients (31% and 19% respectively) and in the group receiving an initial dose of 600 mg than 400 mg (29% and 11% respectively).

**Table 1**

**Response in CML patients in clinical studies**

| | Chronic phase IFN failure (n=532) 400 mg | Accelerated phase (n=235) 600mg n=158 400 mg n=77 | Myeloid blast crisis (n=260) 600 mg n=223 400 mg n=37 |
|---|---|---|---|
| | | % of patients (CI 95%) | |
| **Hematologic response[1]** | **88% (84.9-90.6)** | **63% (56.5-69.2)** | **26% (20.9-31.9)** |
| Complete hematologic response (CHR) | 88% | 28% | 4% |
| No evidence of leukemia (NEL) | Not applicable | 11% | 3% |
| Return to chronic phase (RTC) | Not applicable | 24% | 19% |
| **Major cytogenetic response[2]** | **49% (45.1-53.8)** | **21% (16.2-27.1)** | **13.5% (9.6-18.2)** |
| Complete (confirmed[3]) | 30% (16%) | 14% (4%) | 5% (1%) |

[1]**Hematologic response criteria (all responses to be confirmed after ≥4 weeks):**
CHR: chronic phase study [WBC<10 x$10^9$/L, platelet <450 x$10^9$/L, myelocytes+metamyelocytes <5% in blood, no blasts and promyelocytes in blood, basophils<20%, no extramedullary involvement] and in the accelerated and blast crisis studies [ANC≥1.5 x$10^9$/L, platelets≥100 x$10^9$/L, no blood blasts, BM blasts<5% and no extramedullary disease]
NEL: same criteria as for CHR but ANC≥1 x$10^9$/L and platelets≥20 x$10^9$/L (accelerated and blast crisis studies)
RTC: <15% blasts BM and PB, <30% blasts+promyelocytes in BM and PB, <20% basophils in PB, no extramedullary disease other than spleen and liver (accelerated and blast crisis studies).
BM=bone marrow, PB=peripheral blood
[2]**Cytogenetic response criteria:** A major response combines both complete and partial responses: complete (0% Ph+ metaphases), partial (1-35%)
[3]complete cytogenetic response confirmed by a second bone marrow cytogenetic evaluation performed at least one month after the initial bone marrow study.

The median time to hematologic response was 1 month. Response duration cannot be precisely defined because follow-up on most patients is relatively short interim data. In blast crisis, the estimated median duration of hematologic response is about 6 months. In accelerated phase, median duration of hematologic response is greater than 6 months but cannot yet be estimated. Follow-up is insufficient to estimate duration of cytologic response in all studies.

Efficacy results were similar in men and women and in patients younger and older than age 65. Responses were seen in black patients, but there were too few black patients to allow a quantitative comparison.

# INDICATIONS AND USAGE

GLEEVEC is indicated for the treatment of patients with chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy.

The effectiveness of GLEEVEC is based on overall hematologic and cytogenetic response rates (see Clinical Studies section). There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

# CONTRAINDICATIONS

Use of GLEEVEC is contraindicated in patients with hypersensitivity to imatinib or to any other component of GLEEVEC.

# WARNINGS

**Pregnancy**

Women of childbearing potential should be advised to avoid becoming pregnant.

Imatinib mesylate was teratogenic in rats when administered during organogenesis at doses ≥ 100 mg/kg, approximately equal to the maximum clinical dose of 800 mg/day, based on body surface area. Teratogenic effects included exencephaly or encephalocele, absent/reduced frontal and absent parietal bones. Female rats administered this dose also experienced significant post-implantation loss in the form of early fetal resorption. At doses higher than 100 mg/kg, total fetal loss was noted in all animals. These effects were not seen at doses ≤ 30 mg/kg ( one-third the maximum human dose of 800 mg).

There are no adequate and well-controlled studies in pregnant women. If GLEEVEC is used during pregnancy, or if the patient becomes pregnant while taking (receiving) GLEEVEC, the patient should be apprised of the potential hazard to the fetus.

# PRECAUTIONS

## General

*Fluid retention and edema*: GLEEVEC is often associated with edema and occasionally serious fluid retention (See Adverse Reactions Section). Patients should be weighed and monitored regularly for signs and symptoms of fluid retention. An unexpected rapid weight gain should be carefully investigated and appropriate treatment provided. The probability of edema was increased with higher imatinib dose and age > 65 years. Severe fluid retention (pleural effusion, pericardial effusion,

pulmonary edema, ascites) was reported in 1 to 2% of patients taking GLEEVEC. In addition, severe superficial edema was reported in 1-3% of the patients.

*GI irritation*: GLEEVEC is sometimes associated with GI irritation. GLEEVEC should be taken with food and a large glass of water to minimize this problem.

*Hematologic toxicity:* Treatment with GLEEVEC is often associated with neutropenia or thrombocytopenia. Complete blood counts should be performed weekly for the first month, biweekly fo rthe second month, and periodically thereafter as clinically indicated (for example every 2-3 months). The occurrence of these cytopenias is dependent on the stage of disease and is more frequent in patients with accelerated phase CML or blast crisis than in patients with chronic phase CML. (See DOSAGE AND ADMINISTRATION.)

*Hepatotoxicity:* Hepatotoxicity, occasionally severe, may occur with GLEEVEC (See Adverse Reactions Section). Liver function (transaminases, bilirubin, and alkaline phosphatase) should be monitored before initiation of treatment and monthly or as clinically indicated. Laboratory abnormalities should be managed with interruption and/or dose reduction of the treatment with GLEEVEC. (See DOSAGE AND ADMINISTRATION) Patients with hepatic impairment should be closely monitored because exposure to GLEEVEC may be increased. As there are no clinical studies of GLEEVEC in patients with impaired liver function, no specific advice concerning initial dosing adjustment can be given.

*Toxicities from long-term use:* Because follow-up of most patients treated with imatinib is relatively short (< 6 mos), there are no long-term safety data on Gleevec treatment. It is important to consider potential toxicities suggested by animal studies, specifically, *liver and kidney toxicity and immunosupression.* Severe liver toxicity was observed in dogs treated for 2 weeks, with elevated liver enzymes, hepatocellular necrosis, bile duct necrosis, and bile duct hyperplasia. Renal toxicity was observed in monkeys treated for 2 weeks, with focal mineralization and dilation of the renal tubules and tubular nephrosis. Increased BUN and creatinine were observed in several of these animals. An increased rate of opportunistic infections was observed occur with chronic imatinib treatment. In a 39-week monkey study, treatment with imatinib resulted in worsening of normally suppressed malarial infections in these animals. Lymphopenia was observed in animals (as in humans).

## Drug Interactions

**Drugs that may alter imatinib plasma concentrations**

Drugs that may **increase** imatinib plasma concentrations:

Caution is recommended when administering GLEEVEC with inhibitors of the CYP3A4 family (e.g., ketoconazole, itraconazole, erythromycin, clarithromycin). Substances that inhibit the cytochrome P450 isoenzyme (CYP3A4) activity may decrease metabolism and increase imatinib concentrations. There is a significant increase in exposure to imatinib when GLEEVEC is co-administered with ketoconazole (CYP3A4 inhibitor).

Drugs that may **decrease** imatinib plasma concentrations:

Substances that are inducers of CYP3A4 activity may increase metabolism and decrease imatinib plasma concentrations. Co-medications that induce CYP3A4 (e.g., dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or St. John's Wort) may reduce exposure to GLEEVEC. No specific studies have been performed and caution is recommended.

**Drugs that may have their plasma concentration altered by Gleevec**

Imatinib increases the mean Cmax and AUC of simvastatin (CYP3A4 substrate) 2- and 3.5- fold, respectively, suggesting an inhibition of the CYP3A4 by imatinib. Particular caution is recommended when administering GLEEVEC with CYP3A4 substrates that have a narrow therapeutic window (e.g., cyclosporine or pimozide). Gleevec will increase plasma concentration of other CYP3A4 metabolized drugs (e.g., triazolo-benzodiazepines, dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors, etc.)

Because *warfarin* is metabolized by CYP2C9, patients who require anticoagulation should receive low-molecular weight or standard heparin.

*In vitro*, GLEEVEC inhibits the cytochrome P450 isoenzyme CYP2D6 activity at similar concentrations that affect CYP3A4 activity. Systemic exposure to substrates of CYP2D6 is expected to be increased when co-administered with GLEEVEC. No specific studies have been performed and caution is recommended.

## Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been performed with imatinib mesylate.

Positive genotoxic effects were obtained for imatinib in an *in vitro* mammalian cell assay (Chinese hamster ovary) for clastogenicity (chromosome aberrations) in the presence of metabolic activation. Two intermediates of the manufacturing process, which are also present in the final product, are positive for mutagenesis in the Ames assay. One of these intermediates was also positive in the mouse lymphoma assay. Imatinib was not genotoxic when tested in an *in vitro* bacterial cell assay (Ames test), an *in vitro* mammalian cell assay (mouse lymphoma) and an *in vivo* rat micronucleus assay.

In a study of fertility, in male rats dosed for 70 days prior to mating, testicular and epididymal weights and percent motile sperm were decreased at 60 mg/kg, approximately equal to the maximum clinical dose of 800 mg/day, based on body surface area. This was not seen at doses ≤ 20 mg/kg (one-fourth the maximum human dose of 800 mg). When female rats were dosed 14 days prior to mating and through to gestational day 6, there was no effect on mating or on number of pregnant females. At a dose of 60 mg/kg (approximately equal to the human dose of 800 mg) female rats had significant post-implantation fetal loss and a reduced number of live fetuses. This was not seen at doses ≤ 20 mg/kg (one-fourth the maximum human dose of 800 mg).

## **Pregnancy.** Pregnancy **Category D**. See WARNINGS section.

## Nursing Mothers

It is not known whether imatinib mesylate or its metabolites are excreted in human milk. However, in lactating female rats administered 100 mg/kg, a dose approximately equal to the maximum clinical dose of 800 mg/day based on body surface area, imatinib and/or its metabolites were extensively excreted in milk. It is estimated that approximately 1.5% of a maternal dose is excreted into milk, which is equivalent to a dose to the infant of 30% the maternal dose per unit body weight. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women should be advised against breastfeeding while taking GLEEVEC.

## Pediatric Use

The safety and effectiveness of GLEEVEC in pediatric patients have not been established.

## Geriatric Use

In the clinical studies, approximately 40% of patients were older than 60 years and 10% were older than 70 years. No difference was observed in the safety profile in patients older than 65 years as compared to younger patients, with the exception of a higher frequency of edema. (see PRECAUTIONS) The efficacy of GLEEVEC was similar in older and younger patients.

# ADVERSE REACTIONS

Complications of advanced CML and co-administered medications make causality of adverse events difficult to assess in single arm studies.

The majority of GLEEVEC-treated patients experienced adverse events at some time. Most events were of mild to moderate grade, but drug was discontinued for adverse events in 1% of patients in chronic phase, 2% in accelerated phase and 5% in blast crisis.

The most frequently reported drug-related adverse events were nausea, vomiting, edema, and muscle cramps. (Table 2). Edema was most frequently periorbital or in lower limbs and was managed with diuretics, other supportive measures, or by reducing the dose of GLEEVEC. (See DOSAGE AND ADMINISTRATION.) The frequency of severe edema was 1-5%.

A variety of adverse events represent local or general fluid retention including pleural effusion, ascites, pulmonary edema and rapid weight gain with or without superficial edema. These events appear to be dose related, were more common in the blast crisis and accelerated phase studies (where the dose was 600 mg/day), and are more common in the elderly. These events were usually managed by interrupting GLEEVEC treatment and with diuretics or other appropriate supportive care measures. However, a few of these events may be serious or life threatening, and one patient with blast crisis died with pleural effusion, congestive heart failure, and renal failure.

Adverse events, regardless of relationship to study drug, that were reported in at least 10% of the patients treated in the GLEEVEC studies are shown in Table 2.

285 **Table 2**

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| **Adverse Experiences Reported in Clinical Trials (≥10% of all patients in any trial)[1]** | | | | | | |
|---|---|---|---|---|---|---|
| | Myeloid blast crisis (n= 260) 600 mg n=223 400 mg n=37 (%) | | Accelerated phase (n=235) 600 mg n=158 400 mg n=77 (%) | | Chronic phase, IFN failure (n=532) 400 mg (%) | |
| **Preferred term** | **All grades** | **Grade 3/4** | **All grades** | **Grade 3/4** | **All grades** | **Grade 3/4** |
| Nausea | 68 | 3 | 68 | 5 | 55 | 2 |
| Fluid retention | 67 | 10 | 68 | 6 | 52 | 2 |
| – Superficial edema | 63 | 5 | 66 | 4 | 51 | 1 |
| – Other fluid retention events[2] | 16 | 6 | 9 | 3 | 2 | 0.6 |
| Muscle cramps | 25 | 0.4 | 34 | 0.4 | 46 | 0.9 |
| Diarrhea | 39 | 3 | 49 | 4 | 33 | 0.9 |
| Vomiting | 49 | 3 | 54 | 3 | 28 | 0.9 |
| Hemorrhage | 48 | 16 | 35 | 8 | 13 | 0.4 |
| – CNS hemorrhage | 4 | 2 | 1 | 0.4 | 0.4 | 0.2 |
| – Gastrointestinal hemorrhage | 5 | 2 | 3 | 1 | 0.2 | 0 |
| Musculoskeletal pain | 37 | 8 | 39 | 7 | 27 | 1 |
| Skin rash | 32 | 4 | 39 | 4 | 36 | 3 |
| Headache | 24 | 4 | 26 | 2 | 28 | 0.2 |
| Fatigue | 24 | 2 | 33 | 3 | 25 | 0.2 |
| Arthralgia | 21 | 3 | 26 | 5 | 24 | 0.8 |
| Dyspepsia | 9 | 0 | 19 | 0 | 18 | 0 |
| Myalgia | 7 | 0 | 18 | 2 | 18 | 0.2 |
| Weight increased | 4 | 0.4 | 6 | 1 | 14 | 2 |
| Pyrexia | 38 | 7 | 35 | 7 | 14 | 1 |
| Abdominal pain | 23 | 5 | 26 | 2 | 20 | 0.2 |
| Cough | 12 | 0.8 | 22 | 0.9 | 9 | 0 |
| Dyspnea | 12 | 4 | 16 | 5 | 5 | 0.2 |
| Anorexia | 10 | 2 | 14 | 1 | 3 | 0 |
| Constipation | 13 | 1 | 13 | 0.9 | 4 | 0 |
| Nasopharingitis | 5 | 0 | 10 | 0 | 9 | 0.2 |
| Night sweats | 10 | 0.8 | 10 | 1 | 8 | 0.2 |
| Pruritus | 6 | 1 | 10 | 0.4 | 9 | 0.6 |
| Epistaxis | 12 | 3 | 9 | 0 | 3 | 0 |
| Hypokalemia | 12 | 3 | 9 | 1 | 2 | 0 |
| Petechiae | 10 | 1 | 4 | 0.7 | 0.9 | 0 |
| Pneumonia | 10 | 5 | 7 | 5 | 1 | 0 |
| Weakness | 10 | 3 | 8 | 2 | 5 | 0.2 |

(1) All adverse events occurring in ≥10% of patients are listed regardless of suspected relationship to treatment
(2) Other fluid retention events include pleural effusion, ascites, pulmonary edema, pericardial effusion, anasarca, edema aggravated, and fluid retention not otherwise specified

### Hematologic toxicity:

Cytopenias, and particularly neutropenia and thrombocytopenia, were a consistent finding in all studies, with a higher frequency at doses ≥ 750 mg (phase I study). The occurrence of cytopenias was also dependent on the stage of the disease, with a frequency of grade 3 or 4 neutropenia and thrombocytopenia between 2 and 3 fold higher in blast crisis and accelerated phase compared to chronic phase (see Table 3). The median duration of the neutropenic and thrombocytopenic episodes ranged usually from 2 to 3 weeks, and from 3 to 4 weeks, respectively. These events can usually be managed with either a reduction of the dose or an interruption of treatment with GLEEVEC, but in rare cases require permanent discontinuation of treatment.

### Hepatotoxicity:

Severe elevation of transaminases or bilirubin occurred in 1.1-3.5% (see Table 3) and were usually managed with dose reduction or interruption (the median duration of these episodes was approximately one week). Treatment was discontinued permanently because of liver laboratory abnormalities in less than 0.5% of patients. However, one patient, who was taking acetaminophen regularly for fever, died of acute liver failure.

### Adverse Effects in Subpopulations:

With the exception of edema, where it was more frequent, there was no evidence of an increase in the incidence or severity of adverse events in older patients (≥65 years old). With the exception of a slight increase in the frequency of grade 1/2 periorbital edema, headache and fatigue in women, there was no evidence of a difference in the incidence or severity of adverse events between the sexes. No differences were seen related to race but the subsets were too small for proper evaluation.

**TABLE 3**

**Lab Abnormalities in Clinical Trials**

| | Myeloid blast crisis (n= 260) 600 mg n=223 400 mg n=37 (%) | | Accelerated phase (n=235) 600 mg n=158 400 mg n=77 (%) | | Chronic phase, IFN failure (n=532) 400 mg (%) | |
|---|---|---|---|---|---|---|
| | **Grade 3** | **Grade 4** | **Grade 3** | **Grade 4** | **Grade 3** | **Grade 4** |
| **Hematology parameters** | | | | | | |
| • Neutropenia | 16 | 46 | 24 | 34 | 25 | 8 |
| • Thrombocytopenia | 27 | 31 | 30 | 12 | 16 | <1 |
| • Anemia | 40 | 10 | 31 | 5 | 4 | <1 |
| **Biochemistry parameters** | | | | | | |
| • Elevated creatinine | 1.2 | 0 | 1.3 | 0 | 0 | 0 |
| • Elevated bilirubin | 3.5 | 0 | 1.7 | 0 | 0.4 | 0 |
| • Elevated alkaline phosphatase | 4.6 | 0 | 5.1 | 0.4 | 0.2 | 0 |
| • Elevated SGOT (AST) | 1.9 | 0 | 2.1 | 0 | 1.1 | 0 |
| • Elevated SGPT (ALT) | 2.3 | 0.4 | 3.0 | 0 | 1.7 | 0 |

CTC grades: neutropenia (grade 3 ≥0.5 – 1.0 x$10^9$/L, grade 4 < 0.5 x$10^9$/L), thrombocytopenia (grade 3 ≥10 – 50 x$10^9$/L, grade 4 < 10 x$10^9$/L), anemia (hemoglobin ≥65 – 80 g/L, grade 4 < 65 g/L), elevated creatinine (grade 3 >3-6 x upper limit normal range (ULN), grade 4 >6 xULN), elevated bilirubin (grade 3 >3-10 xULN, grade 4> 10 xULN), elevated alkaline phosphatase (grade 3 >5-20 xULN, grade 4 >20 x ULN), elevated SGOT or SGPT (grade 3 >5-20 xULN, grade 4 >20 xULN)

# OVERDOSAGE

Experience with doses greater than 800 mg is limited. In the event of overdosage, the patient should be observed and appropriate supportive treatment given. An oral dose of 1200 mg/$m^2$/day, approximately 2.5 times the human dose of 800 mg, based on body surface area, was not lethal to rats following 14 days of administration. A dose of 3600 mg/$m^2$/day, approximately 7.5 times the human dose of 800 mg, was lethal to rats after 7-10 administrations, due to general deterioration of the animals with secondary degenerative histological changes in many tissues.

# DOSAGE AND ADMINISTRATION

Therapy should be initiated by a physician experienced in the treatment of patients with chronic myeloid leukemia.

The recommended dosage of GLEEVEC is 400 mg/day for patients in chronic phase CML and 600 mg/day for patients in accelerated phase or blast crisis. The prescribed dose should be administered orally, once daily with a meal and a large glass of water.

Treatment should be continued as long as the patient continues to benefit.

Dose increase from 400 mg to 600 mg in patients with chronic phase disease, or from 600 mg to 800 mg (given as 400 mg twice daily) in patients in accelerated phase or blast crisis may be considered in the absence of severe adverse drug reaction and severe non-leukemia related neutropenia or thrombocytopenia in the following circumstances: disease progression (at any time); failure to achieve

a satisfactory hematologic response after at least 3 months of treatment; loss of a previously achieved hematologic response.

Dose adjustment for hepatotoxicity and other non-hematologic adverse reactions

If a severe non-hematologic adverse reaction develops (such as severe hepatotoxicity or severe fluid retention), GLEEVEC should be withheld until the event has resolved. Thereafter, treatment can be resumed as appropriate depending on the initial severity of the event.

If elevations in bilirubin > 3 x institutional upper limit of normal (IULN) or in liver transaminases > 5 x IULN occur, GLEEVEC should be withheld until bilirubin levels have returned to <1.5 x IULN and transaminase levels to <2.5 x IULN. Treatment with Gleevec may then be continued at a reduced daily dose (i.e. 400→300 mg or 600→400 mg).

Hematologic adverse reactions

Dose reduction or treatment interruptions for severe neutropenia and thrombocytopenia are recommended as indicated in the table 4.

**Table 4**

**Dose adjustments for neutropenia and thrombocytopenia**

| | | |
|---|---|---|
| Chronic phase CML<br>(starting dose 400 mg) | ANC < 1.0 x$10^9$/L<br>and/or<br>Platelets < 50 x$10^9$/L | 1. Stop Gleevec until ANC ≥ 1.5 x$10^9$/L and platelets ≥ 75 x$10^9$/L<br>2. Resume treatment with Gleevec at dose of 400 mg<br>3. If recurrence of ANC < 1.0 x$10^9$/L and/or Platelets < 50 x$10^9$/L, repeat step 1 and resume Gleevec at reduced dose of 300 mg |
| Accelerated phase CML and blast crisis<br>(starting dose 600 mg) | [1]ANC < 0.5 x$10^9$/L<br>and/or<br>Platelets < 10 x$10^9$/L | 1. Check if cytopenia is related to leukemia (marrow aspirate or biopsy)<br>2. If cytopenia is unrelated to leukemia, reduce dose of Gleevec to 400 mg<br>3. If cytopenia persist 2 weeks, reduce further to 300 mg<br>4. If cytopenia persist 4 week and is still unrelated to leukemia, stop Gleevec until ANC ≥ 1 x$10^9$/L and platelets ≥ 20 x$10^9$/L and then resume treatment at 300 mg |
| [1]occurring after at least 1 month of treatment | | |

Pediatric: The safety and efficacy of GLEEVEC in patients under the age of 18 years have not been established.

# HOW SUPPLIED

Each hard gelatin capsule contains 100 mg of imatinib free base.

*100 mg Capsules*

Orange to grayish orange opaque capsule with "NVR SI" printed in red ink.

Bottles of 120 capsules……NDC 0078-0373-66

## Storage

Store at 25° C (77°F); excursions permitted to 15–30°C (59-86°F).

[See USP Controlled Room Temperature]

Dispense in a tight container, USP."

(Date) Printed in U.S.A.

Manufactured by Novartis Pharma AG for:

N O V A R T I S

Novartis Pharmaceuticals Corporation

East Hanover, New Jersey 07936